Materials and Methods

Data collection and curation

We searched all RNA-seq data published in the NCBI Gene Expression Omnibus (GEO) database using the following search terms: Endothel* and human. The search identified 2500 results. We limited to results that included liver endothelial cells or HUVEC. We excluded experiments that did not incorporate at least one untreated control sample and those that did not include any human samples. As a result, we kept the information from 108 HUVEC and 10 HLEC samples **(**Phenotypic characteristics and isolation in **Supplemental Table 8)** organized along 37 experiments **(**GEO accession numbers in **Supplemental Table 9)** [1-32] to proceed with further analysis. For studies that did not make public the read count matrix, the raw fastq files were downloaded and processed according to the ENCODE-DCC pipeline [33, 34], using the STAR [35] aligner and RSEM [36] to obtain gene based read counts.

Bulk RNA-seq normalization and filtering

We filtered genes that had >5 counts in <2 samples, and samples that were outliers for missingness (missing values in >70% of known genes). We additionally filtered genes that had missing values in any sample. This resulted in the inclusion of 11,656 genes and 107 samples in subsequent analysis. Read counts of HUVEC and HLEC were then normalized using a variance stabilizing transformation and a principal component analysis (PCA) was performed as implemented in DESeq2 version 1.34.0 [37].

Single cell RNA-seq data processing

For our project we used two previously performed studies with single cell RNA-seq data, one corresponding to human liver [38] (GSE115469) and the other to atherosclerotic human coronary arteries [39] (GSE131778). The counts matrices were loaded in R version 4.0.4, normalized based on sctransform [40] and clustered with the k-nearest neighbor algorithm as implemented in Seurat [41-44]. Clustering was visualized and identified cell types were compared with the published dataset to confirm concordance. Endothelial cell clusters were identified based on expression of known marker genes (*CDH5, VWF, PECAM1*) [45]. In the liver dataset, the subpopulations of endothelial cells were identified based on gene expression of specific markers (*SPARCL1, TM4SF1, CLEC14A, ID1, IGFBP7* and *VWF* for periportal HLEC, *FCGR2B, S100A13, FCN3, LYVE1, STAB2, CLEC1B, FCN2, CRHBP, STAB1, F8* and *CALCRL* for CV HLEC, *ENG, PECAM1, RAMP3, INMT, DNASE1L3, LIFR, TIMP3, C7* and *CTGF* for portal endothelial cells) as previously described [46].

Cellular deconvolution of bulk RNA-seq

We performed cell type deconvolution of the processed bulk RNA-seq samples using the CIBERSORTx tool [47]. We used a Mixture Matrix formed by the values corresponding to the expression of the genes of the bulk RNA-seq HLEC and HUVEC samples. The Signature Matrix was obtained from single cell RNA-seq of human liver by calculating the average expression (in counts) of the top 2000 variable genes among the endothelial cell clusters. Cell type proportions were then calculated by CIBERSORTx for each of the bulk samples.

Projection of Coronary artery scRNAseq onto Liver scRNAseq dataset

After single cell data normalization, we obtained the subset of cells in single cell RNA-seq of human coronary arteries belonging to endothelial clusters. We then generated corrected low dimensional embeddings and projected the artery endothelial data to the liver single cell UMAP structure using MapQuery in Seurat.

Analysis of the role of CV HLEC and HUVEC in cirrhosis and hepatocellular cancer

To investigate the role of CV HLEC and HUVEC in liver diseases we used two previously published studies with single cell RNA-seq data, one corresponding to healthy and cirrhotic human liver (GSE136103) [48] and the other corresponding to healthy human liver compared to hepatocellular carcinoma (GSE149614) [49]. In both datasets, we normalized the counts data using sctransform as implemented in Seurat. We subsequently integrated the single cell counts data across samples with Seurat using CCA (Canonical Correlation Analysis). We identified the clusters that correspond to each endothelial cell subtype using previously described marker genes (*FCN3, CLEC4G, CRHBP, FCN2, CTSL* and *CLEC1B* for CV HLEC population and *CLEC14A, CPE, SRPX, CTNNAL1, CD320* and *RFK* for periportal HLEC population) and estimated the proportion of cells corresponding to each cluster among all the cells in each sample. We then compared proportions between healthy and diseased samples using a Wilcoxon rank sum test with a two-tailed alternative hypothesis **(Supplemental figure 1B)**.

Differential expression analysis

We used DESeq2 to normalize the gene expression results using a size factor that accounts for library size and gene size. Differential expression (DE) was tested based on a negative binomial Wald statistic with a two-tailed alternative hypothesis as implemented in DESeq2, using identified surrogate variables from SVA as covariates. We separately compared CV HLEC and periportal HLEC (based on CIBERSORTx results) to HUVEC. A corresponding p-value was generated from the Wald statistic and adjusted for multiple testing using false discovery rate (FDR). Genes were considered significant if their FDR was < 0.05. Gene set enrichment analysis was performed using the GSEA package [50, 51]. Each gene's negative binomial Wald statistic as the ranking parameter for GSEA, and the rank list was tested against the HALLMARK gene sets available in MSigDB [52]. Gene sets were considered significant if their FDR was < 0.05.

Cell culture

Human umbilical vein endothelial cells (HUVECs) and Human liver endothelial cells (HLEC) were purchased from Lonza (Basel, Switzerland). Cells were cultured on collagen-coated plates in EGM-2 media (Lonza) in 37 °C with 5% CO2. Endothelial cells were purchased at passage 2 and all experiments were performed within five passages. For our experiments, 30000 cells per well of HUVEC and FCGR2B+ sorted HLEC of the same passage were cultured in collagen-coated p12 well plates and grew simultaneously under the same conditions. 24 hours prior to the planned experiments, the media were replaced with 1ml of fresh media. Supernatants and cells were collected the next day.

Fluorescence Activated Cell Sorting or FACS

HLECs were cultured and expanded as described above. Cells were lifted with trypsin, centrifuged and resuspended in HBSS, 10ul of FCGR2B-FITC conjugated antibody (ab134384, Abcam, Cambridge, UK) was used per million of cells. Cells were incubated in rotation in the dark at 4°C for 30 minutes. Three washes with HBSS were performed before resuspending the cells in 1ml of HBSS and filtering through a 45mm matrix to remove clumps. Propidium Iodide was used to mark dead cells just before sorting. All steps were performed on ice. FACS sorting was performed with a Beckman Coulter MoFlo XDP (California, US). Cells without antibody were processed in the same conditions as negative control to gate only the FCGR2B+ HLEC. The negative fraction corresponding to FCGR2B- viable cells was also gated and sorted as FCGR2B- HLEC.

Quantitative real-time PCR:
Total RNA was isolated from cells (RNeasy kit from Qiagen following the manufacturer's protocol). The A260/A280 ratio of all samples was between 1.9 and 2.1 as measured by spectrophotometry (NanoDrop; Thermo Scientific). 50 ng of RNA were used for a one step qPCR reaction performed with TaqMan probes (following the manufacturer´s instructions) on an CFX Connect thermal cycler (Bio-Rad). The qPCR probes Hs00166654_m1 *SERPINC1*, Hs01084593_g1 *CCNB2*, Hs00938777_m1 *CDK1*, Hs00185645_m1 *XPO1*, Hs01079643_g1 E2F8, Hs03023943_g1 ACTB, Hs00252034_m1 F8, Hs0098443_m1 F10, Hs00165590_m1 PROS1, Hs01109446_m1 *VWF*, Hs006054557_m1 *E2F3* were from Thermo Fisher Scientific (Massachusetts, US). Quantification was performed in triplicate for each sample. Expression results were calculated by the ΔΔCT method and were normalized to the reference gene *ACTB*. Statistical analysis was done by two-tailed unpaired Student's t-test and a $p < 0.05$ was considered significant.

Enzyme-linked immunosorbent assay (ELISA)
Protein S and Factor X levels in media were measured by commercially available antibody duo ELISA and standard curve was made by their commercially available substrates performing fold dilution starting at [200ng/ml] (Enzyme Research Labs Inc, South Bend, IN) according to the manufacturer's instructions. Undetectable samples were assigned a value of the lower limit of detection/2 (0.05 ng/mL). The levels of VWF antigen in media were measured by an ELISA using antibodies from Fitzgerald Industries (20R-VG001, 60R-VG002hrp). Statistical analysis was done by two-tailed unpaired Student's t-test and a $p < 0.05$ was considered significant.

Factor VIII Activity assay

Factor VIII activity levels in cell supernatants were detected by the adaptation of the commercially available plasma FVIII Chromogenic kit, Chromogenix Coatest® SP Factor VIII (Diapharma). We followed the manufacturer's protocol, and we performed the assay in microplates doing a 4 fold reduction of all volumes keeping all other conditions. The supernatants were analyzed without dilution and we included a reference curve that was prepared by diluting a human plasma pool (sigma: P9523-1ml) in the cell culture medium (ECM complete). Absorbance was read at 405 nm and at 490 nm using a SpectraMax M5 Microplate Reader. Subtraction of measurements at 490 nm corrected for absorbance differences between wells.

Expression of *VWF* and *F8* in different endothelial cell types

From the 2500 results obtained after searching for Endothel* and human in the NCBI Gene Expression Omnibus (GEO), we filtered to results that included endothelial cells, and we excluded experiments that did not incorporate at least one untreated control sample and those that did not include any human samples. This process resulted in the following GEO accession numbers that we included in subsequent analyses **(Supplemental Table 7)** [6-30, 53-69] . The resulting information was processed and normalized to get the matrix of gene expression in reads per kilobase per million (RPKM), and the results were plotted.

Discovery of transcription factors and subsequent analysis

We prioritized potential transcription factor (TF) drivers of the differences in the CV HLEC and HUVEC transcriptome using a heuristic approach combining RNA-seq results with motif enrichment. Specifically, we used HOMER [70] to identify novel motifs that were enriched in promoters of genes that were either upregulated or downregulated in CV HLEC compared to HUVEC at an FDR < 0.05. We limited the results to motifs that were enriched at a p-value < 1e-11 as per the HOMER software recommendations. We further limited the results to the top four TFs which were assigned to each of the significant motifs by HOMER with a probability at least 0.6. To ensure that we remove false positives, as recommended by HOMER, we manually evaluated the alignments of each of the known TF motifs to the de novo motif and removed TFs whose motif core did not align to the de novo motif. We compared the resulting list to TFs which were significantly differentially expressed in CV HLEC compared to HUVEC and prioritized TFs that showed transcriptional changes concordant with the observed motif enrichment (for example, an activating TF was prioritized if their motif was enriched in upregulated genes in CV HLEC and their expression was also significantly increased in the same group, whereas a repressing TF was prioritized if their motif was enriched in downregulated genes in CV HLEC and their expression was also significantly increased in the same group).

RNA interference

E2F8 was silenced by transfecting HUVEC with siRNA targeting human *E2F8* (Thermo fisher scientific). We used 50 nM non-targeting siRNA (si-Control) or *E2F8*-targeting siRNA (si-E2F8). Transfection was performed with Lipofectamine siRNA max (Invitrogen) according to the manufacturer's instructions. Gene silencing was confirmed by RT-qPCR of cell extracts isolated 48 h post transfection. Supernatants were collected after treatment with media or 10 µM histamine for 1 h, and the concentration of VWF released into the media was measured by ELISA as previously described.

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